



UNITED STATES ENVIRONMENTAL PROTECTION
AGENCY WASHINGTON, DC 20460

OFFICE OF CHEMICAL
SAFETY AND POLLUTION
PREVENTION

November 7, 2017

MEMORANDUM

Subject: Efficacy Review for HYG-25,
EPA Reg. No. 1706-EUU;
DP Barcode #: 440695
E-Submission #: 18573

From: Sophie Nguyen
Efficacy Evaluation Team
Product Science Branch
Antimicrobials Division (7510P)

A handwritten signature in black ink, appearing to read "S. Nguyen", is located to the right of the "From:" field.

Thru: Kristen Willis, Acting Team Leader
Efficacy Evaluation Team
Product Science Branch
Antimicrobials Division (7510P)

A handwritten signature in black ink, appearing to read "Kristen Willis", is located to the right of the "Thru:" field.

To: Demson Fuller RM 32 / Donna Kamarei
Regulatory Management Branch II
Antimicrobials Division (7510P)

Applicant: Nalco Water, an Ecolab Company
1601 W Diehl Road
Naperville, IL 60563-1198

Formulation from the Label:

| <u>Active ingredient:</u> | <u>% by Weight</u> |
|---------------------------------|--------------------|
| Sodium Chlorite | 25% |
| <u>Other ingredients:</u> | 75% |
| <u>Total</u> | 100% |

I. BACKGROUND

The product, HYG-25 (EPA Reg. No. 1706-EUU), is a new product formulated as a chlorine dioxide precursor for microbial control such as suspended *Legionella*, macrofouling control, mollusk control, and chemical oxidation in water and wastewater and papermill water. The product is designed to be a secondary potable water treatment. The applicant is submitting a registration application for the new end use product. The protocol titled Standard Operating Procedure for Measuring Antimicrobial Efficacy in Secondary Potable Water System was submitted by Ecolab for review and deemed acceptable by the Agency on January 21, 2016. The efficacy study was conducted at Accuratus Lab Services, 1285 Corporate Center Drive, Suite 110 Eagan, MN 55121.

The data package contained a letter to EPA (dated February 20, 2017), EPA form 8570-1 (Application for Pesticide Registration), EPA form 8570-4 (Confidential Statement of Formula), EPA form 8570-27 (Formulator's Exemption Statement), EPA form 8570-34 (Certification with Respect to Citation Data), EPA Form 8570-35 (Data Matrix), 1 new efficacy study (MRID No. 50199804), and the proposed product label dated July 12, 2017. Statement of No Data Confidentiality Claims, Statement of Good Laboratory Practice Compliance, and Quality Assurance Statement were included with each study.

II. USE DIRECTIONS

Directions for Use in the Mechanical or Electrolytic Generation of Chlorine Dioxide:

HYG-25 may be used in the mechanical or electrolytic generation of chlorine dioxide. HYG-25 is fed to chlorine dioxide generation equipment, which produces an aqueous solution of chlorine dioxide by one of the following methods of generation:

- (1) The chlorine method, which uses HYG-25 and chlorine gas;
- (2) The hypochlorite method, which uses HYG-25 and a combination of a hypochlorite solution, and an acid;
- (3) The acid-chlorite method, which uses HYG-25 and an acid as the activating agent; or,
- (4) The electrolytic method which uses HYG-25 with sodium chloride added as needed.

Your Nalco Sales Engineer can guide you in the selection, installation and operation of generation systems. Consult the instructions on the chlorine dioxide generation system before using HYG-25.

SECONDARY TREATMENT OF POTABLE WATER SYSTEMS:

Chlorine dioxide is used as an antimicrobial agent in drinking water treatment and can be used as part of an overall program for the reduction of suspended *Legionella pneumophila*. The required dosages will vary depending on application conditions and the degree of contamination present. For secondary treatment of potable water systems, a chlorine dioxide residual concentration of 0.09 - 0.75 ppm is sufficient for antimicrobial treatment and suspended *Legionella pneumophila* reduction. Monitor the system to ensure that the chlorite concentration does not exceed its maximum contaminant level (MCL) of 1 ppm and that chlorine dioxide does not exceed its maximum residual disinfection level (MRDL) of 0.8 ppm. Residual chemistry and byproducts must be monitored as required by the National Primary Drinking Water Regulations (40 CFR Part 141), EPA Safe Drinking Water Act, and state drinking water standards.

Chlorine dioxide can serve as an important part of the program for the reduction of *Legionella* bacteria in potable water systems. A residual concentration of 0.09 ppm chlorine dioxide has been

shown in laboratory testing to reduce *Legionella pneumophila* ATCC 33152 (strain Philadelphia-1) bacteria within 30 minutes following intermittent dosage. Under actual operating conditions, chemical treatment alone may not be an effective approach for *Legionella* control, risk mitigation from LDB or for the prevention of Legionnaires' disease.

POTABLE WATER TREATMENT:

Chlorine dioxide is used as a disinfectant in drinking water treatment. The required dosages will vary depending on water conditions and the degree of contamination present. For most municipal and public potable water systems, a chlorine dioxide residual concentration of 0.05 - 0.75 ppm is sufficient to provide disinfection. Typically, a dose of up to 2 ppm is needed to obtain the target residual chlorine dioxide levels in the water system. Monitor the distribution system to ensure that the chlorite concentration does not exceed its maximum contaminant level (MCL) of 1 ppm and that chlorine dioxide does not exceed its maximum residual disinfection level (MRDL) of 0.8 ppm. Residual disinfectant and disinfection byproducts must be monitored as required by the National Primary Drinking Water Regulations (40 CFR Part 141) and state drinking water standards.

III. AGENCY STANDARDS FOR PROPOSED CLAIMS

Protocol titled "Standard Operating Procedure for Measuring Antimicrobial Efficacy in Potable Water Systems" (MRID #49741801), was reviewed and deemed acceptable under Protocol Review titled "1706PA4_D430459_Nalco Company_SOP for Measuring Antimicrobial Efficacy in Potable Water System" (dated January 21, 2016). The review concluded that the submitted protocol was adequate for evaluating the efficacy of secondary potable water treatment methods against *Legionella pneumophila* and others. However, the treatment contact time period is not to exceed 30 minutes.

IV. SYNOPSIS OF SUBMITTED EFFICACY STUDY

According to the HYG-25_1706-EUU_Technical Review Response_20170707_CBI document dated July 7, 2017, the responses were as follow:

- a. Question: Certificates of Analysis for the tested lots were not provided for evaluation. Please report the concentrations of Sodium chlorite in the tested lots.

Answer:

[REDACTED]

The concentration of sodium chlorite used to produce the tested lots is provided in the table below:

| Batch #ClO2 Tested | % Sodium Chlorite |
|--------------------|-------------------|
| DDM0906161 | 24.96% |
| DDM0906162 | 25.32% |
| DDM0906163 | 24.79% |

- b. Question: The report indicates that 0.75 ml of test substance was used. Please report the concentrations of the test substance and the identity of the test substance.

Answer: The test substance identity, as indicated on page 7 of the GLP report, is chlorine dioxide. The stock concentration of the test substance (chlorine dioxide) was 100 ppm+/-

20%. During the testing procedure, 0.75 ml of the test substance was diluted as reported in the table on page 9 of the GLP report.

- c. Question: The label indicates 4 methods for chlorine dioxide generation. Please report which method was used and how chlorine dioxide was generated in the data submitted.

Answer: The four methods listed on the submitted label are the commercial/field based methods for generation of chlorine dioxide from sodium chlorite. All of these chlorine dioxide production methods could utilize the same EPA registered sodium chlorite precursor (EPA Reg. No. 1706-EUU) without any impact to the efficacy of the produced chlorine dioxide. To facilitate this efficacy testing, the acid chlorite method was used to produce lab scale quantities of chlorine dioxide.

- d. Question: The residual chlorine dioxide concentrations resulted after 30 minutes that were indicated in the data do not reflect the label claims of efficacy at 0.05 - 0.75 ppm residual chlorine dioxide. The efficacious concentration claimed on the label should reflect the minimum effective concentration tested.

Answer: Thank you for identifying this discrepancy. This was a carry-over from our pre-GLP data. We agree with the EPA assessment and have corrected the lower limit on the label for 1706-EUU to reflect the efficacy test results (see attached).

According to the HYG-25_1706-EUU_Technical Review Response_20170707_CBI document dated July 26, 2017, the responses were as follow:

- e. Question: Is there a user manual for this product? If so, can you please send us a PDF copy?

Answer: Attached are the operating manuals for two Nalco Water ClO₂ generation devices. The AccuCide device is based on the common acid - chlorite method and the Envirox device is based on the electrolytic method. Both devices currently operate using an EPA registered sodium chlorite precursor (EPA Reg.# 5382-43-1706 or# 21164-6-1706) for production of chlorine dioxide. These devices would also be used for production of chlorine dioxide using the product currently under review for registration (EPA Reg.# 1706-EUU).

Please note that Nalco Water considers the information in the AccuCide and Envirox user manuals to be confidential business information and requests that they are not included with the HYG-25 registered label that is uploaded to PPLS.

- f. Question: Can you please provide/expand on the 4 methods of chlorine dioxide generation on page 3 of the label?

Answer: Chlorine dioxide (ClO₂) is a neutral chlorine compound that has a high water solubility but is very volatile and is characterized by lack of hydrolysis in water and remains as a dissolved gas. Since ClO₂ can be explosive under pressure, it is not practical to be compressed, stored commercially, or transported at concentrations utilizable for larger water treatment applications and must be generated on-site for most microbial control applications. There are several different methods for on-site ClO₂ generation. A compilation of the different technical methods can be reviewed in Table 4-1 (page 4-5) of the **EPA Office of Water Guidance Document on Alternative Disinfectants and**

Oxidants (April 1999), see below. Most of these technical methods utilize sodium chlorite as a precursor for ClO₂. Most common of these is the acid-chlorite method where an acid and chlorite precursors are simply mixed to produce ClO₂. Since ClO₂ must be generated on-site, different water treatment companies have developed devices (generators) that utilize one or the other of these technical methods to produce ClO₂ at the application/treatment site in order to meet the system demand and specific site requirements. These chemical generation devices (other than the electrochemical method) act to simply provide a mixing environment for the different precursor chemistries such as the chlorite and the acid in a liquid flowing stream. The intent of each generation method through any of these devices is to produce ClO₂ at an effective concentration for adequate microbial control. The produced antimicrobial, ClO₂, through any of these devices would have the same properties and microbial control efficacy. Since the same EPA registered sodium chlorite precursor can be utilized to generate ClO₂ through the different generation devices, Nalco Water includes four possible use generation methods on their registered product labels. [REDACTED]

It should be noted that for laboratory evaluation of the properties of chlorine dioxide, such as microbial efficacy testing, it is not feasible to provide a generation device for production of a small quantity of ClO₂. Therefore, laboratory methods have been developed based on the widely used acid-chlorite method that utilize the same principle and technical reactions but allow for production of small quantities of ClO₂ in a beaker. In a laboratory environment, this produced ClO₂ solution can then be stored refrigerated or frozen in amber colored bottles for extended periods of time for subsequent use in efficacy testing.

- 1. MRID 50199804 “Standard Operating Procedure for Measuring Antimicrobial Efficacy in Secondary Potable Water Treatment” Test Organisms: *Legionella pneumophila* (ATCC 33152), for HYG-25 (EPA Reg. No. 1706-EUU), by Matthew Sathe, Study conducted at Accuratus Lab Services. Study completion date – October 19, 2016. Project Number: A21699; Ecolab GLP Study Number: 1600010CL1.**

This study was conducted against *Legionella pneumophila* (ATCC 33152). Three batches (Nos. DDM0906161, DDM0906162, and DDM0906163) of the product, HYG-25 (EPA Reg. No. 1706-EUU), were tested according to Accuratus Lab Services Protocol No. ECO01040516.CUST. The potable water used as test water was prepared from standard tap water from a city water faucet. The test water was autoclave sterilized at 121°C to deplete any chlorine present, and the water was allowed to cool at room temperature. The test substance dosage providing 0.68 – 0.83 ppm chlorine dioxide was determined prior to preparing the test substance for testing. The dosage for each batch was evaluated separately. To determine the dose, a sample of sterilized deionized water was placed into a flask, and test substance was added to the water with following amounts:

| Test Substance Batch | Test Substance Added | Deionized Water | Chlorine Dioxide Hach Result |
|----------------------|----------------------|-----------------|------------------------------|
| DDM0906161 | 1.00 mL | 99.0 mL | 1.08 ppm* |
| | 0.75 mL | 99.25 mL | 0.83 ppm |
| DDM0906162 | 0.75 mL | 99.25 mL | 0.82 ppm |

| | | | |
|------------|---------|----------|----------|
| DDM0906163 | 0.75 mL | 99.25 mL | 0.80 ppm |
|------------|---------|----------|----------|

*Dose was out of range and was not used

From each prepared 100.0 mL of the test substance, a 1.00 mL aliquot was removed to achieve 99.0 mL of test substance for testing. Each flask was placed in a water bath at 20.1°C and equilibrated for ≥ 10 minutes. Each flask was then assayed for residual chlorine dioxide at 5, 15, and 30 minutes using the Hach DPD titration kit (Table 1 in Results).

A loopful of *Legionella pneumophila* was streaked to BCYE agar plates, inoculated and incubated for 2 days at 35-37°C in 6.0% CO₂. 5.0 mL of deionized water was added to each plate to dislodge the growth. The culture was diluted in deionized water further to target a minimum of 1×10^9 CFU/mL. Each flask containing the test substance was swirled to create a residual motion of liquid, and 1.00 mL aliquot of culture was added midway between the center and edge of the surface. Each flask was swirled to mix the contents and was exposed for the 5 minute, 15 minute, and 30-minute exposure times at 20.1°C. Following exposure, 1.00 mL of the inoculated substance was transferred to 9 mL of neutralizer (Lethen Broth + 0.07% Lecithin + 0.5% Tween 80). The neutralized contents corresponded to the 10-1 dilution. Serial dilutions were prepared and 1.00 mL of 10^{-1} and 10^{-1} to 10^{-4} was plated in duplicate. A 10.0 mL aliquot of the inoculated test substance was removed from the flask and tested for free residual oxidant using the Hach DPD titration method. All subcultures plates were incubated for 5 days at 35-37°C, in CO₂. Following incubation, the subculture plates were visually examined for growth. Controls included those of purity, sterility, numbers control, and neutralization confirmation.

Note:

Protocol Amendment: Per Sponsor's request, the protocol is amended to include Ecolab GLP study number 1600010 for the performance of stability testing of the chlorine dioxide use-solution generated from HYG-25.

The protocol is amended to remove the * symbol on page 8 in the Exposure Temperature section as there is no applicable footnote and this is a typographical error.

Protocol Deviation: The protocol states that a test substance sterility control will be performed, however due to the test substance preparation instructions stating to prepare 100 mL, there was not enough test substance to perform this control and it was not performed, resulting in the deviation. Since this control is for informational purposes with no acceptance criterion, and the test/controls did not demonstrate any contamination, this deviation has no impact on the study.

V. RESULTS

Table 1:

| Results | | | | | Carrier Population CFU/mL (Avg. Log ₁₀) |
|-----------------------|-------------|-----------------------------------|--|-----------------------------|---|
| Batch # | Replicate # | Residual chlorine dioxide reading | CFU/mL (Average log ₁₀) | Log ₁₀ Reduction | |
| 5-minute contact time | | | | | |
| DDM0906161 | 1 | 0.40 ppm | <1.00 x 10 ² (<2.00) | >5.21 | 1.6 x 10 ⁷ (7.21) |
| | 2 | 0.46 ppm | | | |
| DDM0906162 | 1 | 0.50 ppm | <1.00 x 10 ² (<2.00) | >5.21 | |
| | 2 | 0.51 ppm | | | |
| DDM0906163 | 1 | 0.46 ppm | <1.00 x 10 ² (<2.00) | >5.21 | |
| | 2 | 0.27 ppm | | | |

| 15-minute contact time | | | | | |
|------------------------|---|----------|------------------------------------|---------|------------------------------|
| DDM0906161 | 1 | 0.22 ppm | $<1.00 \times 10^2$ (<2.00) | >5.21 | 1.60×10^7 (7.20) |
| | 2 | 0.33 ppm | | | |
| DDM0906162 | 1 | 0.36 ppm | $<1.00 \times 10^2$ (<2.00) | >5.21 | |
| | 2 | 0.35 ppm | | | |
| DDM0906163 | 1 | 0.29 ppm | $<1.00 \times 10^2$ (<2.00) | >5.21 | |
| | 2 | 0.15 ppm | | | |
| 30-minute contact time | | | | | |
| DDM0906161 | 1 | 0.14 ppm | $<1.00 \times 10^2$ (<2.00) | >5.21 | 1.70×10^7 (7.23) |
| | 2 | 0.20 ppm | | | |
| DDM0906162 | 1 | 0.22 ppm | $<1.00 \times 10^2$ (<2.00) | >5.21 | |
| | 2 | 0.20 ppm | | | |
| DDM0906163 | 1 | 0.18 ppm | $<1.00 \times 10^2$ (<2.00) | >5.21 | |
| | 2 | 0.09 ppm | | | |

VI. CONCLUSION

The submitted efficacy study **supports** the use of the product, HYG-25 (EPA File No. 1706-EUU), as a chlorine dioxide precursor. The study supports the product as a secondary potable water treatment against *Legionella pneumophila* (ATCC 33152) at 0.27 – 0.51 ppm residual ClO₂ after 5-minute contact time, at 0.15 – 0.36 ppm ClO₂ after 15-minute contact time, and at 0.09 – 0.22 ppm ClO₂ after 30-minute contact time. Results demonstrated a reduction of 5-log in the periods of 5-, 15-, and 30-minute contact times at 20.1°C. Purity controls were reported as pure. Sterility controls did not show growth. Neutralization confirmation testing showed growth.

VII. LABEL RECOMMENDATIONS (for proposed label dated 2017-07-12)

- The proposed label claims are acceptable regarding the use of the product, HYG-25 (EPA File No. 1706-EUU), a secondary potable water treatment against *Legionella pneumophila* (ATCC 33152) when dosed up to 2 ppm chlorine dioxide to produce a residual chlorine dioxide concentration of 0.09 – 0.75 ppm after 30-minute to be used in the following proposed methods:
 - Nalco's AccuCide System: The acid-chlorite method, which uses AccuVator 100A, an acid mixture, to produce an aqueous solution of chlorine dioxide gas.
 - Nalco's Envirox SRE1000 and SRE2000: an electrochemical method that uses an electrochemical cassette to produce an aqueous solution of chlorine dioxide.
 - A non-specific hypochlorite method that uses the product and a combination of a hypochlorite solution and an acid to produce an aqueous solution of chlorine dioxide.
 - A non-specific chlorine method that uses the product and chlorine gas to produce an aqueous solution of chlorine dioxide.
- The concentration of Sodium chlorite used on-site to produce Chlorine dioxide for treatment should not exceed 25% nominal concentration as claimed on the CSF and proposed label.
- On page 4 of the proposed label, revise 0.05 – 0.75 ppm to 0.09 – 0.75 ppm residual chlorine dioxide concentration under Potable Water Treatment.

4. On page 4 of the proposed label, qualify “bacteria” under the heading “GENERAL INDUSTRIAL COOLING AND PROCESS WATER TREATMENT” to indicate non-pathogenic bacteria. Please specify non-pathogenic bacteria for all claims for industrial cooling and process water treatment.
5. Municipal drinking water must meet the requirements of the Safe Drinking Water Act (42 U.S.C. 300f). Label claims and directions, as well as testing and performance requirements, must be acceptable to the Office of Drinking Water of the EPA, and appropriate documentation of such acceptance must be submitted. Please refer to EPA’s [Guidance on Disinfectant Products Intended to Treat Drinking Water](#) to ensure that the product meets both FIFRA and SDWA standards.
6. Please provide more information concerning the claims for effectiveness of product at pH between 3-11 and at pH greater than 10 or remove these claims from the label. Data were not generated to substantiate these claims. Office of Water’s Guidance Document on Alternative Disinfectants and Oxidants (April 1999) states that more “research is needed to further clarify how pH impacts the effectiveness of chlorine dioxide”.
7. Please provide more information concerning the claim for effectiveness of product in presence of ammonia, oil or organic contamination in cooling water or drinking water systems or remove related claims from the label. Data were not generated to substantiate this claim. Additionally, efficacy related claims cannot be used in conjunction with cooling water treatment, since the agency currently does not have efficacy testing standards for this use.
8. For the AccuCide System manual, [REDACTED]
[REDACTED]
[REDACTED]
9. Registrant should comply with the recommendations specified in Office of Water’s Guidance Document on Alternative Disinfectants and Oxidants (April 1999) for chlorine dioxide monitoring, disinfection byproduct control strategies, and overall equipment operation, maintenance, and monitoring of application to ensure that the product is continuously efficacious when used with the proposed chlorine dioxide generators.